



the BrainSTORM Consortium, Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Walters, R. K., Bras, J., Duncan, L., Escott-Price, V., Falcone, G. J., Gormley, P., Malik, R., Patsopoulos, N. A., Ripke, S., Wei, Z., Yu, D., Lee, P. H., Turley, P., Grenier-Boley, B., Chouraki, V., ... Dunn, E. (2018). Analysis of shared heritability in common disorders of the brain. *Science*, 360(6395), [eaap8757].  
<https://doi.org/10.1126/science.aap8757>

Peer reviewed version

Link to published version (if available):  
[10.1126/science.aap8757](https://doi.org/10.1126/science.aap8757)

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## Introduction

Disorders of the brain can exhibit considerable epidemiological comorbidity and share symptoms, provoking debate about their etiologic overlap. However, detailed study of phenotypes with different ages of onset, severity and presentation presents a considerable challenge. Recently developed heritability methods allow us to accurately measure correlation of genome-wide common variant risk between two phenotypes from pools of different individuals, to understand how connected they, or at least their genetic risks, are on the genomic level. We quantified the degree of overlap for genetic risk factors of 25 common brain disorders, based on genome-wide association data for 215,683 patients and 657,164 controls, as well as 17 phenotypes from a total of 1,191,588 individuals.

## Rationale

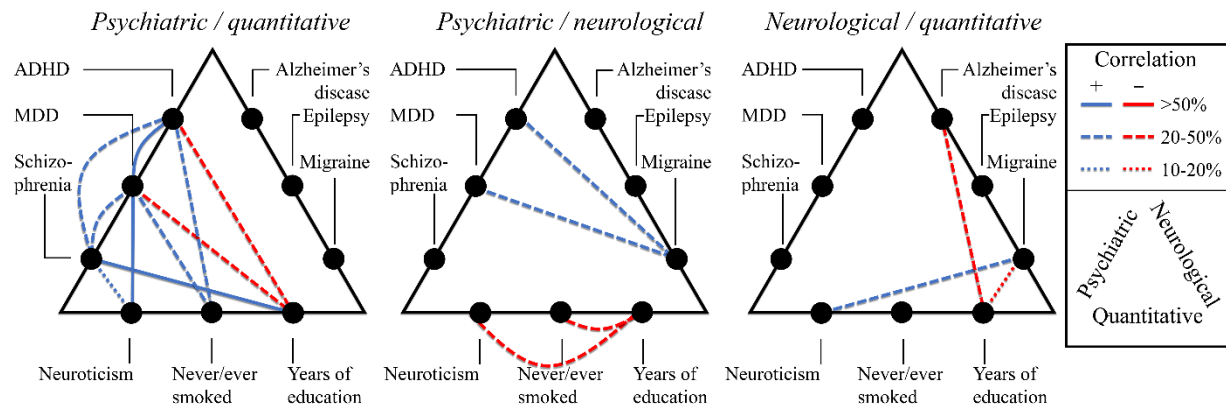
The classification of brain disorders has evolved over the last century, reflecting the medical and scientific communities' assessments of the presumed root causes of clinical phenomena such as behavioral change, loss of motor function, or alterations of consciousness. Directly observable phenomena (such as the presence of emboli, protein tangles, or unusual electrical activity patterns) generally define and separate neurological disorders from psychiatric disorders. Understanding the genetic underpinnings and categorical distinctions for brain disorders and related phenotypes may inform the search for their biological mechanisms.

## Results

Common variant risk for psychiatric disorders was shown [to](#) correlate significantly, especially between ADHD, bipolar disorder, major depressive disorder (MDD) and schizophrenia. In contrast, neurological disorders appear more distinct from one another and from the psychiatric disorders, except for migraine, which was significantly correlated to ADHD, MDD and Tourette Syndrome. We demonstrate that the personality trait neuroticism in the general population is significantly correlated with almost every psychiatric disorder and migraine. We also identify significant sharing between disorders and early life cognitive measures in the general population (e.g. years of education and college attainment), demonstrating positive correlation with several psychiatric disorders (e.g. anorexia nervosa and bipolar disorder) and negative correlation with several neurological phenotypes (e.g. Alzheimer's disease and ischemic stroke), even though the latter are considered to result from specific processes that occur later in life. Extensive simulations were also performed to inform how power, diagnostic misclassification and phenotypic heterogeneity influence genetic correlations.

## Conclusion

The high degree of genetic correlation among many of the psychiatric disorders adds further evidence that the current clinical boundaries among them do not reflect distinct underlying pathogenic processes, at least on the genetic level. This suggests a deeply interconnected nature, in contrast to neurological disorders, and underscores the need to refine psychiatric diagnostics. Genetically informed analyses may provide important 'scaffolding' to support such restructuring of psychiatric nosology, which likely requires incorporating many levels of information. In contrast, we find limited evidence for widespread common genetic risk sharing among neurological disorders or across neurological and psychiatric disorders. We show that both psychiatric and neurological disorders have robust correlations with cognitive and personality measures. Further study is needed to evaluate whether overlapping genetic contributions to psychiatric pathology may influence treatment choices. Ultimately, such developments give hope to reducing heterogeneity and eventually improving the diagnosis and treatment of psychiatric disorders.



**Figure Caption**

**Subsection of genetic risk correlations among brain disorders and quantitative phenotypes.**

Heritability analysis of brain disorders points to pervasive sharing of genetic risk among psychiatric disorders, largely absent among neurological disorders, but present from both groups to neuro-cognitive quantitative phenotypes. Only significant correlations shown. Color and line solidity indicate direction and magnitude of correlation, respectively. ADHD – attention deficit hyperactivity disorder; MDD – major depressive disorder.